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(54) Title: PHARMACEUTICAL COMPOSITIONS HAVING APPETITE REDUCING ACTIVITY AND A PROCESS FOR THEIR PREPARATION

(57) Abstract

Pharmaceutical compositions having appetite reducing activity. The compositions contain (5α,6α)-7,8-didehydro-4,5-epoxy-17-(2-propanyl)-morphinane-3,6-diol.

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Pharmaceutical compositions having appetite reducing activity and a process for their preparation

Background of the invention

One of the basic phenomenon of life is that the living creatures take food from their environment. As a basic phenomenon is concerned, it has been risen simultaneously with the rise of life. Considering that for the living creatures both overfeeding and underfeeding are dangerous, simultaneously with the rise of the food intake also a system for controlling the food intake has been risen. Together with the development of life also this system became more and more developed and today it operates as a very complicated system "having several regulating circles". (A summary of some presumed and proved regulating mechanisms is given in The Lancet of February 19, 1983 on pages 398 to 401.) One of these regulating mechanisms is based on the so called opioid endogenic peptides. This is supported by the observation that if a special opiate antagonist, naloxone [(5 α)--4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-morphinane-6--one] is administered to animals it is absorbed by the opiate receptors and thereby the food intake, the appetite and also the fluid intake of the animal is hindered. The observation that by the administration of endogenic (and exogenic) opiates the appetite of animals and humans can be increased shows that these compounds exert an influence on the nutrition (Am. J. Clin. Nutr., 35, 757-761, 1982 and Appetite, 2, 193-208, 1981).

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While in case of non-domesticated animals the regulating mechanisms function more or less properly and ensure the appropriate food intake of the animals, in case of humans of ten lesions deriving from overfeed emerge.

This can be readily understood as on the one hand in case of humans food intake is caused not only by the sensation of hunger and, on the other hand the degree of the food intake does not follow the demands of the organism, the demands are often many time surpassed. It is true that by proposeful food intake obesity can be avoided but in many instances the decision in itself is not sufficient for changing the alimentary habits, for carrying out the decision a medical support is necessary as well.

The best known slimming agents are desopimone (4--chloro-α,α-dimethyl-phenethylamine), gracidine (3--methyl-2-phenyl-morpholine) and teronac [5-(p-chloro--phenyl)-2,5-dihydro-3H-imidazo[2,1-a]isoindole-5-ol).

Unfortunately the known slimming agents have several contraindications and side effects, so in case of a great part of the patients requiring treatment these agents cannot be used.

The side effects of desopimone are the dilatation of the pupil, increase of the inner pressure of the eyes, vomiting, diarrhoea, abdominal pains, difficulty at the beginning of urination, headache, allergic exanthema, vertigo; and insomnia and nervosity as well as somnolence and sedative effect appear in about equal proportions.

Gracidine only with increased care can be administered in case of obesity associated with heart diseases, cardiovascular troubles and hypertension. At the intake of gracidine and when it is administered continuously during

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the cure driving of vehicles, working above ground and on dangerous machines are prohibited. During its use and influence, respectively, also the take of alcoholic drinks is prohibited. According to new informations the compositions containing gracidine are forbidden.

Teronac may cause mouth dryness, headache, nervosity, nausea, constipation, impairment of sleep, dizziness, tachycardia, reversible trouble of sexual functions, sweating, eczema, dilatation of the pupil, allergy. Also in case of glaucoma, heart-rhythm troubles, serious cardiac failure, renal insufficiencies, liver troubles, hypertensions, cerebral processes, psychiatric diseases, gastric and intestinal ulcers it is contraindicated.

On the basis of the aforesaid an appetite reducing composition is needed which does not show the side effects of the known compositions and which can be widely used without side effects.

As the active ingredient of a composition like this primarily those substances can be taken into consideration which exert their influence on the field of the central nervous system. Substances of this type are also the opiate antagonists mentioned above.

It is known that on obese people the food intake is reduced by naloxone (J. Clin. Endocrin. Metab., 55, 196-198, 1982). It has the similar activity in Prader-Willi syndrome (The Lancet, 1980, 876-877), traumatic hypothalamic hyperphagia (Am. J. Clin. Nutr., 35, 757-761, 1982) and also in case of healthy patients rendered hungry by 2-desoxy-glucose infusion.

The use of naloxone as active ingredient in appetite reducing compositions is unavoidable hindered by the fact that when administered per os it should be

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given in extremely high doses. But in case of a widely used appetite reducing composition only the peroral administration can come into consideration.

The object of the present invention is to provide an appetite reducing composition which can be widely used without side effects and contraindications.

Brief description of the invention

The object of the present invention is attained by an appetite reducing composition cintaining as active ingredient nalorphine [(5α, 6α)-7,8-didehydro-4,5-epoxy--17-(2-propenyl)-morphinane-3,6-diol]. This composition can be administered perorally and rectally.

Detailed description of the invention

According to the present invention nalorphine, preferably in the form of its salt prepared with a strong acid, such as a mineral acid, e.g. hydrochloric acid, hydrobromic acid is formulated into pharmaceutical compositions with carriers, diluents, flavouring, aromatizing, colouring agents and other auxiliary materials normally used for the preparation of oral or rectal pharmaceutical compositions.

The pharmaceutical compositions of the present invention are prepared in the form of tablets, dragées, pilules, capsulated or chartulated powder compositions and various solutions, suspensions (such as liquid medicines, drops etc.), suppositories.

According to a preferred embodiment of the invention one dosage unit or a low number of the dosage units (tablet, dragée, chartula, capsule, suppository, drop or spoonful amount) of the pharmaceutical composition contain

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the single dose. A dosage unit may contain of course more doses, in this case for example the tablets may be provided with dividing cuts in order to facilitate their break into pieces.

The daily dose of the active ingredient is 15 to 30 mg. As the active ingredient is long since used as an antinarcotic, the actual dose can be easily determined by the physician on the basis of his skill, considering the individual reactivity and tolerance of the patient and the effect intended to be achieved. These doses may exceed the doses mentioned above or may be less than indicated. The daily dose may be divided into more single doses containing equal or different amounts of the active ingredient. Thus the constant active ingredient level can be easily ensured.

The invention relates to a process for reducing the appetite of humans or animals as well, wherein the effective dose of the composition of the present invention, e.g. the amount containing 15 to 30 mg of the active ingredient is administered to the person or to the animal to be treated.

It has been surprisingly found that during or after the treatment carried out with the pharmaceutical composition of the present invention side effect (mouth dryness) attributable to the composition only very rarely and in a very mild form was observed. No side effect was observed which could have been connected to the narcotic effect of the opium derivatives. No dependence on the medicine has been risen, no habituation or withdrawal symptom was observed after the treatment.

The invention is illustrated by the following non limiting examples.

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Example 1

Tablet containing 5 mg of active ingredient

A powder mixture of the following composition is prepared:

nalorphine hydrobromide	5.0 g
colloidal silica	1.0 g
magnesium stearate	3.0 g
talc	9.0 g
microcrystalline cellulose	82.0 g
	100.0 g

From the powder mixture thus obtained after homogenisation tablets each weighing 100.00 mg are compressed under a pressure of 49-785 MPa (500-8000 kp/cm^2).

Example 2

Tablet containing 10 mg of active ingredient

A powder mixture of the following composition is prepared:

nalorphine hydrobromide	10.0 g
colloidal silica	1.0 g
magnesium stearate	3.0 g
talc	9.0 g
microcrystalline cellulose	77.0 g
	100.0 g

From the powder mixture thus obtained after homogenisation tablets each weighing 100.00 mg are compressed under a pressure of 49-785 MPa (500-8000 kp/cm^2).

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Example 3

Tablet containing 20 mg of active ingredient

A powder mixture of the following composition is prepared:

nalorphine hydrobromide	20.0 g
talc	3.0 g
magnesium stearate	4.0 g
mannitol	108.0 g
	135.0 g

From 15.0 g of starch and water a 3-5 % granulating liquid is prepared. The powder mixture is granulated with the starch solution thus obtained. Granules having a diameter of about 1 mm are prepared. The granules are dried at a temperature of 50°C, then they are compressed under a pressure of 49-785 MPa (500-8000 kp/cm^2) into tablets each weighing 150.00 mg.

Example 4

Suppository containing 20 mg of active ingredient

A suppository mass of the following composition is prepared:

nalorphine hydrobromide	2o.0 g
suppository base (cocoa butter)	1980.0 g
	2000.0 g

The suppository base is melted at 37-38°C, the active ingredient is uniformly distributed therein, then the mass is filled into suppository forms suitable for preparing suppositories of 2 g and it is cooled.

Clinical tests were carried out on obesed voluntary patients with the tablets containing 5 mg of active ingredient prepared according to Example 1. The body

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weight was measured at the beginning and at the end of the test, the number of the tablets administered daily was also registered and at the end of the treatment the weight loss was calculated in the dimension of kg/week. The following Table contains the data thus obtained together with the occasional side effects.

Table

Number of patient	Body weight at admission	Body weight at discharge	Weight loss (kg/week)	Number of tablets per day	Side effect
1.	103.5 kg	100.5 kg	0.75	2	mouth dryness
2.	92.0 kg	84.5 kg	1.07	1	ø
3.	82.0 kg	76.0 kg	0.50	3	ø
4.	80.0 kg	78.0 kg	0.66	3	ø
5.	123.0 kg	122.0 kg	0.50	5	ø
6.	87.0 kg	85.0 kg	1.0	3	ø
7.	80.0 kg	77.0 kg	0.75	2	ø
8.	84.0 kg	79.0 kg	0.83	2	ø
9.	114.0 kg	108.0 kg	0.75	3	obstipation
10.	78.0 kg	72.0 kg	1.0	4	thirst
11.	100.0 kg	87.0 kg	2.1	3	obstipation
12.	90.0 kg	82.0 kg	0.5	4	obstipation
13.	114.0 kg	98.0 kg	0.7	3	obstipation
14.	92.0 kg	81.5 kg	0.7	4	obstipation
15.	124.0 kg	108.0 kg	0.8	3	ø
16.	97.0 kg	88.0 kg	0.4	5	ø
17.	75.0 kg	68.0 kg	0.7	6	transitorial vertigo
18.	103.0 kg	99.0 kg	0.5	5	ø
19.	83.0 kg	75.0 kg	1.0	4	transitorial nausea

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Number of patient	Body weight at admission	Body weight at discharge	Weight loss (kg/week)	Number of tablets per day	Side effect
20.	96.0 kg	77.0 kg	1.1	3	obstipation
21.	91.0 kg	87.0 kg	0.5	4	ø
22.	86.0 kg	75.0 kg	1.5	5	obstipation
23.	104.0 kg	93.0 kg	0.5	4	ø
24.	78.0 kg	72.0 kg	0.7	4	ø
25.	109.0 kg	100.0 kg	0.9	4	obstipation
26.	119.0 kg	106.0 kg	1.0	4	ø
27.	97.3 kg	87.3 kg	1.0	4	ø
28.	82.5 kg	76.0 kg	0.6	3	ø
29.	126.2 kg	115.0 kg	1.3	3	obstipation
30.	81.5 kg	73.8 kg	1.1	3	ø
31.	83.0 kg	75.0 kg	0.8	3	obstipation
32.	108.6 kg	101.3 kg	0.8	3	transitorial vertigo sleepiness
33.	119.8 kg	112.0 kg	0.8	4	obstipation
34.	115.0 kg	110.5 kg	0.9	4	obstipation
35.	98.0 kg	87.0 kg	1.2	3	ø
36.	97.0 kg	90.0 kg	1.1	3	ø
37.	115.5 kg	100.3 kg	2.1	3	ø
38.	125.0 kg	102.5 kg	1.3	3	ø
39.	132.0 kg	121.0 kg	0.7	4	ø

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Claims:

1. Pharmaceutical compositions having appetite reducing activity characterized in that they contain 5 to 30 mg of (5α, 6α)-7,8-didehydro-4,5-epoxy-17-(2-propenyl)-morphinane-3,6-diol per dosage unit or a salt thereof formed with a strong acid together with a carrier, diluent, flavouring, aromatizing, colouring agent and other auxiliary material normally used for the preparation of oral or rectal pharmaceutical compositions.

2. The pharmaceutical compositions of claim 1 characterized in that they are formulated into solid compositions suitable for oral administration.

3. The pharmaceutical compositions of claim 1 characterized in that they are formulated into suppository compositions suitable for rectal administration.

4. Process for the preparation of pharmaceutical compositions having appetite reducing activity characterized in that 5 to 30 mg of (5α,6α)-7,8-didehydro-4,5-epoxy-17-(2-propenyl)-morphinane-3,6-diol per dosage unit or a salt thereof formed with a strong acid is formulated into a pharmaceutical composition together with a carrier, diluent, flavouring, aromatizing, colouring agent and other auxiliary material normally used for the preparation of oral or rectal pharmaceutical compositions.

5. The process of claim 4 characterized in that solid pharmaceutical compositions, preferably tablets are prepared using solid auxiliary materials.

6. The process of claim 4 characterized in that suppository compositions are prepared using semi-liquid auxiliary materials.

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7. Process for treating mammals, such as humans in order to reduce their appetite and thereby their body weight characterized in that a pharmaceutical composition containing 5 to 30 mg of (5α,6α)-7,8-didehydro-4,5-epoxy-17-(2-propenyl)-morphinane-3,6-diol is administered daily to mammals, such as humans preferably in the form of its salt formed with a strong acid.

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INTERNATIONAL SEARCH REPORT

International Application No PCT/HU 84/00042

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.[4]: A 61 K 31/485

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
IPC[4]	A 61 K 31/485

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
X	DE, A, 2 923 955 (TECNOFARMACI S.P.A.) 24 January 1980 (24.01.80), see claims 1-3, page 11, lines 6-15.	(1,2,4,5)
X	US, A, 4 267 182 (J.W. HOLADAY, A.J. FADEN) 12 May 1981 (12.05.81), see abstract, column 2, lines 26-30, 43-63.	(1,2,4,5)
A	WO, A, 82/03 768 (THE UNIVERSITY OF KENTUCKY RESEARCH FOUNDATION) 11 November 1982 (11.11.82), see example 5, composition B, claims 1,4,9,14.	(1,4)
Y	EP, A, 0 005 636 (E.J. DU PONT DE NEMOURS & CO) 28 November 1979 (28.11.79), see abstract, page 2, lines 1-16, page 13.	(1,2,4,5)
Y	S.G. Holtzman 'Life Sciences', volume 16, published 1975, by Pergamon Press (Oxford, New York, Braunschweig), see pages 1465-1470, especially page 1465, second passage, page 1466, sixth passage, page 1467, last passage, page 1468, fig. 1, fourth passage, last passage of the discussion	(1,2,4,5)

* Special categories of cited documents: [15]

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IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
26 September 1984 (26.09.84)	16 October 1984 (16.10.84)
International Searching Authority [1]	**Signature of Authorized Officer [20]**
AUSTRIAN PATENT OFFICE	

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [10]

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers 7, because they relate to subject matter [12] not required to be searched by this Authority, namely:

Method for treatment of the human or animal body by therapy - see Article 17(2)(a)(i) and Rule 39

2. [ ] Claim numbers ....., because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [13], specifically:

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [11]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the International application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the International application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Anhang zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

Annex to the International Search Report on International Patent Application No. PCT/HU 84/00042

Annexe au rapport de recherche internationale relatif à la demande de brevet international n°.

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned International search report. The Austrian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

La présente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche internationale visé ci-dessus. Les renseignements fournis sont donnés à titre indicatif et n'engagent pas la responsabilité de l'Office autrichien des brevets.

Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
DE-A-2 923 955	24/01/1980	BE-A1- 876 968	01/10/1979
		FR-A1-2 428 439	11/01/1980
		ZA-A - 79-2 923	30/07/1980
US-A-4 267 182	12/05/1981	None	
WO-A-82/03 768	11/11/1982	AU-A1-85 247/82	24/11/1982
		EP-A1-0 077 393	27/04/1983
EP-A-0 005 636	28/11/1979	PT-A - 69 628	01/05/1979
		-B-	21/10/1981
		BE-A1- 876 382	19/11/1979
		DK-A - 2 059/79	20/11/1979
		FI-A - 79-1 591	20/11/1979
		JP-A2- 55-382	05/01/1980
		LU-A - 81 294	05/06/1980
		PH-A - 15 271	02/11/1982
		AU-B2- 526 854	03/02/1983

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